EXHIBIT 17

Neurodevelopmental Effects of Antiepileptic Drugs

Kimford J. Meador, MD

Address
Department of Neurology, Medical College of Georgia, 1120 15th Street (BA3410), Augusta, GA 30912, USA.
E-mail: kmeador@neuro.mcg.edu

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Although the vast majority of children born to women with epilepsy are normal, these children are at increased risk for both anatomic and cognitive impairments. Current evidence suggests that the defects are the result of in utero antiepileptic drug (AED) exposure combined with a genetic predispositon. However, the exact mechanisms underlying these effects remain to be delineated. AED polytherapy increases the risk, but it remains uncertain if specific AEDs pose an overall greater threat. Most women with epilepsy cannot avoid AEDs during pregnancy because of the greater risks posed by seizures to the mother and fetus. Therefore, current recommendations emphasize definitive diagnosis and the use of AED monotherapy at the lowest effective dose if treatment is indicated. Prenatal folate and multivitamins should also be given routinely to women of childbearing age who require AED therapy.

Introduction

Antiepileptic medications are frequently used by women of childbearing age for epilepsy and other indications. Epilepsy is a common neurologic disorder affecting 0.6% to 1% of the population [1]. Approximately 7.6 to 12.7 million women in the United States have epilepsy, and 24,000 births per year are to women with epilepsy (using the more conservative estimate of epilepsy prevalence). Unlike the situation with drugs of abuse, the large majority of women with epilepsy cannot abstain from antiepileptic drugs (AEDs) due to the risks that seizures pose to the woman and her unborn child. Approximately 95% of women with epilepsy in the United States are on AEDs [2], so about 22,800 children per year are exposed in utero to AEDs (not including those women on AEDs for reasons other than epilepsy).

Although the risks of birth defects and neurodevelopmental deficits are increased in the children of women with epilepsy, recent consensus guidelines emphasize the increased risk of polytherapy, but could not delineate which of the AEDs is the most teratogenetic based on available data [3,4]. Further, there is a lack of consensus concerning the relative risks across different AEDs of impaired psychomotor development from in utero exposure. Several prior reviews of somatic and behavioral development of children of mothers with epilepsy are available [5,6]. The present review updates these prior reports by briefly outlining the risks of anatomic defects and focusing primarily on the possible behavioral teratogenicity of AEDs.

Anatomic Teratogenicity of Antiepileptic Drugs

All of the older AEDs are established teratogens [5]. The risk of congenital malformations in the general population is 2% to 3%, and the risk in children of women with epilepsy has been estimated to be approximately 4% to 6%. The wide range of reported incidences has left some uncertainty as to the exact risk. A recent study examined children at birth from 128,049 pregnancies in Boston from 1986 to 1993 [7••]. This study found major malformations in 4.5% of the children of women with epilepsy treated with AED monotherapy, and 8.6% of those treated with AED polytherapy. The risk for children of women with epilepsy who were not treated with AEDs did not differ from healthy control patients. In contrast, the risk for children of women without epilepsy who were treated with AEDs was the same as the children of women with epilepsy who were exposed to AEDs. These results are important because they highlight the teratologic role of AEDs in these patients and confirm the incidence of birth defects in the children of women with epilepsy, including the increased risk of polytherapy.

The most common major anatomic abnormalities attributed to AEDs include heart malformations (*eg*, ventral septal defect), oro-facial defects (*eg*, cleft lip or palate), urologic defects (*eg*, hypospadius), bony abnormalities, growth retardation, and neural tube defects (*eg*, spina bifida) [5,6]. Neural tube defects have been linked to two specific AEDs, with a 1% to 2% risk for valproate and a 0.5% to 1% risk for carbamazepine. In addition, in utero AED exposure has been associated with minor dysmorphisms such as epicanthal folds, hypertelorism, broad/flat nasal bridge, upturned nose, and distal digital hypoplasia. Although several of the newer AEDs have favorable teratogenic

profiles in animals, there is inadequate human data to discern if the same profile will hold true for children exposed in utero. Even for the older AEDs, there is inadequate data to determine if the overall teratogenicity of certain AEDs is less than others.

Behavioral Teratogenicity of Antiepileptic Drugs

Although there is great individual variation, children of women with epilepsy exhibit cognitive/behavioral developmental delay as a group compared with the general population. A variety of factors may contribute to the observed behavioral deficits in children of women with epilepsy. These factors include AEDs, seizures during pregnancy, seizure type, heredity, maternal age/parity, and socioeconomic status. Data from animals and humans suggest that AEDs play an important role in this regard. However, animal data cannot be directly extrapolated to humans, and design flaws in human studies preclude firm conclusions. Further, the critical question as to whether there are differential effects of in utero AED exposure on neurodevelopment remains unresolved. Thus, important information is missing as to the appropriate management of women who require AED therapy.

Animal studies

Behavioral neurodevelopmental consequences of prenatal AED exposure have not been as extensively investigated as AED-induced somatic abnormalities, but behavioral effects are known to occur at dosages below those associated with somatic malformations and at blood levels similar to human therapeutic levels [8,9]. In utero phenobarbital in mice produces neuronal deficits, reduces brain weight, and impairs development of reflexes, open-field activity, schedule-controlled behavior, and catecholamine brain levels [10–12]. Phenytoin alters critical genes and delays neurodevelopment [13]. Prenatal phenytoin in rats produces significant behavioral abnormalities (*eg*, impaired learning and motor coordination) at dosages lower than would produce anatomic defects (100 to 200 mg/kg) and at maternal levels (10 to 25 μg/mL) overlapping the human therapeutic range [14,15]. In utero primidone also produces behavioral-impairment deficits in rats [16], and less pronounced neurobehavioral effects have been seen as a result of trimethadione (250 mg/kg) or valproate (150 to 200 mg/kg) exposures [14]. Neuronal membranes in the hippocampus are altered by phenytoin and valproate [17,18]. Prenatal exposure to phenytoin, but not carbamazepine or stiripentol, produces hyperexcitability in monkeys [19]. Because animal studies can control for a variety of confounding factors, they suggest that in utero AEDs may produce neurobehavioral deficits at dosages not associated anatomic malformations. However, direct extrapolation of animal results to humans is not possible because of interspecies differences and the lack of comparative information on pharmacokinetics and developmental outcomes.

Human studies

Reduced head circumference (microcephaly) has been found in newborns exposed to AEDs, and is associated with impaired psychomotor development [20]. Prenatal exposure to phenobarbital, phenytoin, primidone, or carbamazepine has been linked to reduced head circumference at birth [21,22]. However, several other studies have either found no microcephaly or attributed it to factors other than AED exposure [23,24].

Most investigations have reported an increased risk of developmental delay in children of mothers with epilepsy [25]. Multiple factors could contribute to the observed differences, but animal studies suggest that AEDs play a role. Consistent with this view, the incidence of mental retardation is increased in children of mothers with epilepsy, but not in children of fathers with epilepsy [26]. Further, in women with epilepsy who do not take an AED during pregnancy, their children exhibit no deficits in intelligence or physical features compared with matched control subjects [27]. Little data are available for AED effects in children of nonepileptic women. In small samples, in utero phenobarbital had no effect [23], but benzodiazepines were associated with cognitive impairments [28]. In children of mothers with epilepsy, the risk of mental retardation has been related to intrauterine growth retardation, major malformations, numerous minor malformations, in utero AED exposure, increased dose and numbers of AEDs, decreased parental education, impaired maternal-child relation, maternal partial-seizure disorder, and number of seizures during pregnancy [29–31]. However, the relationship with AED exposure has not been constant [32]. Disparities across studies are due in part to differences in methodology. Formal assessments of mental performance were not necessarily made, and they were rarely blinded as to AED exposure. In many "prospective" studies, subjects were enrolled postnatally. The influences of other disease and non–disease-related factors have not been controlled in an empirical fashion. Although inheritance is an important predictor of cognitive abilities, parental intelligence quotients (IQs) have rarely been used in these studies. Only one study has measured IQ values in both parents; mothers with epilepsy and their children had lower IQs, but the fathers did not differ, compared with control patients [33]. However, that study did not address differential AED effects.

In a study following children from birth, intellectual function was assessed at 4 to 8 years of age in 20 children exposed in utero to phenytoin and 98 control children who had been identified at birth as having three or more minor abnormalities [34]. The examiner was unaware of the exposure status. The phenytoin group had significantly lower IQ scores (109 ± 11) compared with control subjects

(118 ± 12). The results suggests that phenytoin may cause behavioral teratogenic effects on children, but the study lacked controls for parental IQ.

Two studies from Denmark [34,35] examined the effects of in utero phenobarbital exposure on intelligence in adult men of mothers without epilepsy. Men exposed prenatally to phenobarbital had significantly lower verbal IQ scores than predicted (approximately 7 IQ points or 0.5 SD). Lower socioeconomic status and an "unwanted" pregnancy markedly increased the deficit to a difference of 20 IQ points. Similar interactive adverse effects are well documented in the mental retardation literature. Although these two studies are not definitive, they suggest that behavioral teratogenetic sequelae of prenatal phenobarbital exposure in humans can continue into adulthood, and that socioeconomic and psychologic factors may interact with drug exposure to exacerbate the cognitive deficits.

From 1991 to 1994, 353 pregnant mothers at risk for premature delivery were randomized to receive placebo or phenobarbital plus vitamin K to investigate the possible prevention of intracranial hemorrhage [36]. The total median dose of phenobarbital was 1.6 g administered over 4 days. Subsequently, behavioral outcomes were assessed in 121 of the children at 2 years of age using the Bayley Mental Developmental Index (MDI) [36]. Children of the mothers randomized to phenobarbital had significantly lower MDI (104 ± 21; n=59) compared with the placebo group (113 ± 22; n=62). Although the results are consistent with the study from Denmark, only 32% of the total randomized children were tested at the 2-year-old follow-up. Thus, the validity of the results remains in doubt.

The greatest controversy and most critical unanswered question is whether differential AED effects exist. A comparative study of children exposed to carbamazepine and phenytoin reported adverse effects of phenytoin on neurobehavioral development, but none for carbamazepine [37]. However, a significantly greater proportion of the carbamazepine group included nonepileptic mothers, and the mean maternal AED dose was less for carbamazepine: 534 mg/d (range, 800 to 1200 mg/d) versus 354 mg/d (range, 300 to 400 mg/d) for phenytoin. When the correct statistical analyses are performed comparing the difference scores of the two groups of children, no significant difference between AEDs is present. Finally, maternal IQ was not used in the analyses, but IQ differences between the maternal and children groups for the two AEDs were actually of the same magnitude. Thus, design flaws preclude conclusions from this study.

The preliminary report of another comparative study noted differential AED effects [38]. Children aged 6 to 16 years were recruited from a sample identified at birth, and included children exposed in utero to carbamazepine, phenobarbital, and phenytoin, as well as matched controls (*ie*, age, sex, race, and parental socioeconomic status). Neuropsychologic testing revealed that the phenobarbital-exposed children had a full-scale IQ that was 11 points lower than matched controls, that carbamazepine-exposed children had a verbal IQ that was 10 points lower, and that the phenytoin-exposed group did not differ from its control group. Further details and confirmation in a separate cohort is needed.

A recent retrospective study from England raises concern that another AED might pose special cognitive risks [39•]. Special education needs were assessed in 594 school-age children born to women with epilepsy, and the percentages for each AED group were as follows: no drug was 11%; monotherapy with valproate was 30%; monotherapy with carbamazepine was 3%; other monotherapy was 6%; polytherapy with valproate was 24%; and polytherapy without valproate was 16%. Thus, the risk of special education needs appears to be elevated for valproate. However, the results require replication because subject selection bias cannot be ruled out. If the same pattern of results were to be found in a completely separate cohort from a different country, it would provide striking evidence that the observation is genuine.

In summary, children of women with epilepsy are at increased risk for cognitive impairment. However, it remains unclear if there are differential effects across AEDs. Ultimately, a well-controlled prospective study will be required to resolve this important issue. The results of such a study would have direct impact on the management of women with epilepsy.

Possible Mechanisms of Antiepileptic Drug Effects on Neurodevelopment

The adverse effects of a teratogen require a susceptible genotype, and this may involve interaction of multiple genes [40]. Supporting this concept is the observation that dizygotic twin fetuses exposed to phenytoin may have discordant outcomes [41]. AED dosages lower than those required to produce anatomic abnormalities can result in functional deficits, so it is unclear if functional and anatomic defects involve similar mechanisms. Several mechanisms for the functional teratogenicity of AEDs have been proposed, including neuronal suppression, folate-related mechanisms, *N*-methyl-D-aspartate (NMDA)/gamma-aminobutyric acid (GABA)-related mechanisms, ischemia/hypoxia, and reactive intermediates (*eg*, epoxides and free radicals).

Neuronal suppression

Because AEDs may suppress neuronal irritability, they may also reduce neuronal excitation, which might result in altered synaptic growth and connectivity. These adverse effects in the early stages of neurodevelopment might cause long-term deficits in cognition and behavior.

Folate mechanisms

Folate is involved in DNA and RNA synthesis, so it is not surprising that its demands are increased during pregnancy. Phenobarbital, phenytoin, and primidone can deplete folate, and valproate changes folate metabolism [25]. In addition, blood folate concentrations have been found to be lower in women with epilepsy who have abnormal pregnancy outcomes [42]. Folate treatment has been reported to reduce malformation rates in mice exposed in utero to phenytoin [43], but these results have been challenged [44].

N-methyl-D-aspartate/gamma-aminobutyric acid-related mechanisms

Animal studies of fetal alcohol syndrome have demonstrated that the untoward effects of in utero exposure to ethanol are mediated via a dual mechanism that includes blockade of NMDA glutamate receptors and activation of GABA-A receptors [45•]. The effect of ethanol exposure is at a maximum in the third trimester and causes widespread apoptotic neurodegeneration that results in reduced brain mass and neurobehavioral deficits. Because many AEDs affect NMDA and GABA mechanisms, it is possible that AEDs may produce similar effects. However, no studies have been conducted to confirm or refute this mechanism in AEDs.

Ischemia/hypoxia

Ischemic-induced embryopaty in animals resembles phenytoin-induced defects, and hyperoxic chamber treatment may reduce the phenytoin malformations [46]. However, it is likely that the resemblance of ischemic effects to AED defects is due to the fact that ischemia induces free radicals.

Reactive intermediates

The fetotoxicity of some AEDs may be mediated not by the parent compound, but by toxic intermediary metabolites.

Epoxides

Because epoxides are highly reactive arene oxide intermediates, they can bind to nucleic acids. Inhibition of epoxide hydrolase, which can detoxify arene oxides, can lead to an increase in malformations [47]. Low epoxide-hydrolase activity in the aminocytes of children exposed to phenytoin has been related to dysmorphic features [48]. However, this theory has been questioned because conversion of an AED to an epoxide requires P450 enzymes, which are not expressed in embryonic tissues [49]. If the epoxide had to be formed by the maternal enzymes, it is unlikely that it would reach the fetus before binding to maternal tissues.

Free radicals

In contrast to epoxies, free radical reactive intermediates may be formed from AEDs by bioactivation via embryonic prostaglandin H synthetase or lipoxygenases, which are active in the fetus [50]. The formation of these reactive oxygen species in the fetus could then result in binding to DNA, protein, or lipids, leading to teratogenesis. Supporting this hypothesis, phenytoin-induced teratogenic defects are reduced by prostaglandin H synthetase inhibitors, free radical trapping agents, antioxidants (*eg*, vitamin E), and antioxidative enzymes (*eg*, superoxide dismutase).

Principles of Antiepileptic Drug Use in Preconception and Pregnancy

Detailed recommendations are available from both the American Academy of Neurology and the American College of Obstetric and Gynecologic Physicians [3,4]. First, confirmation of the diagnosis and need for AED treatment should be confirmed. If treatment is indicated, then AED monotherapy should be employed if possible, with the AED given at the lowest effective dose. The patient should receive counseling on the increased risks to pregnancies in women with epilepsy, but this advice should be balanced by the fact that the large majority of children born to these mothers are normal. Present data do not allow delineation of which AED is the drug of choice during pregnancy. Thus, drug selection is based on choice of the AED that provides the best seizure control with the fewest side effects. All women of childbearing age taking AEDs should receive folic acid supplementation of 0.4 to 5 mg/d. If there is a history of neural tube defects in prior pregnancies or in the family, an AED other than carbamazepine or valproate should probably be considered. During pregnancy, maternal serum α-fetoprotein and a level II (anatomic) ultrasound should be considered at 14 to 18 weeks to detect major defects. Some AEDs have been shown to increase the risk of hemorrhage in the early postnatal period. Thus, the mother should receive 10 mg/d of vitamin K during the last month of pregnancy, and the child should receive 1 mg intramuscularly at birth.

Conclusions

The majority of children born to women with epilepsy are normal, but these children are at increased risk for anatomic and cognitive impairments. The risks appear to be primarily related to AED exposure. However, the differential effects of AEDs are uncertain. Furthermore, the magnitude of cognitive and behavioral effects is uncertain. In addition, the mechanisms underlying these effects remain to be delineated.

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